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(12) **Patent:** (11) **CA 670254**

(54) MASTITIS COMPOSITION

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ABSTRACT:

CLAIMS: Show all claims

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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This invention relates to a composition for use in the treatment of mastitis.

Various mastitis treating compositions have been proposed in the past. Most of such formulations include penicillin. However, penicillin is frequently found in residual amounts in the milk of cows treated for mastitis. Since many people are sensitive to minute amounts of penicillin the presence of the residual penicillin in the milk is undesirable.

While it has previously been proposed to prepare aerosol compositions for combatting respiratory diseases comprising solid streptomycin or dihydrostreptomycin and a nontoxic pressure generating propellant, see U.S. Elder patent 2,802,772, in such procedure the aerosol is simply sprayed into the atmosphere. The use of liquid aerosols is stated by Elder as being ineffective for his purpose. It will be appreciated that the problem of infusing a mastitis treating composition into the mammary gland through the relatively restricted teat opening is in no way analogous to such broadcast spraying for treatment of respiratory diseases of chickens and the like.

It is an object of the present invention to develop a mastitis treating composition which does not utilize penicillin.

Another object of the invention is to prepare an aqueous mastitis treating composition which can be infused into the udder of a cow.

A further object is to prepare novel aerosol compositions.

An additional object is to devise an improved method for introduding an antibiotic through a relatively restricted body opening.

Still further objects and the entire scope of applicability of the present invention will become apparent from the detailed description given hereinafter; it should be understood, however, that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

It has now been found that these objects can be attained by the preparation and use of certain aerosol antibiotic compositions. The preferred composition is an aqueous dispersion of dihydrostreptomycin, neomycin and polymyxin B.

In place of dihydrostreptomycin there can be used streptomycin and there can also be used other forms of polymyxin. The dihydrostreptomycin, neomycin and polymyxin B can be utilized as either the free base or as the sulfate or other nontoxic salt, e.g., the hydrochloride.

While the mastitis treating compositions set forth above are preferred, in some instances such as where milk containing penicillin may be discarded, it is also intended within the scope of this invention to include penecillin in the formulation for the treatment of mastitis. The amount of penicillin to be employed in such case is relatively small, consequently the loss of milk may not be economically prohibitive.

Aqueous aerosol compositions can be made also from compositions which include sulfa drugs, e.g., sulfamerazine, sulfathiazole and sulfanilamide, tyrothricin and other agents presently being used in mastitis preparations.

While it is preferred to use an aqueous base there can be employed other nontoxic liquids, e.g., peanut oil, sesame oil, mineral oil, Plastibase (a mixture of 95% liquid petrolatum and 5% solid polyethylene). The liquid vehicle should be milk miscible. The term aqueous base is intended to include milk itself since milk can be successfully employed as the vehicle in the aerosol.

The presently preferred pressure generating propellant in the aerosol is nitrous oxide. Other nontoxic gaseous propellants which can be used include nitrogen, carbon dioxide and the gases known under the Registered Trade Mark "Freon" (dichlorodifluoromethane, trichlorofluoroethane, and trichlorofluoromethane).

It is presently preferred to use a pressure of 90lbs/sq. in. in the aerosol package although this pressure can be varied as is well known in the aerosol art, e.g., pressures of 25 to 150 psig can be used.

In the preferred composition according to the invention there is employed

dihydrostreptomycin (or streptomycin)	50 mg. to 1,000mg.
Neomycin	50 mg. to 500 mg.
Polymyxin	50,000 units to 1,000,000 units
Water	2.5 cc.

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The exact amount of water is not critical but a 2.5 cc. dosage has been found convenient for infusing cows with the composition. Thus there can be used 1 to 30 cc. of water.

Example 1

Dihydrostreptomycin	2,500 mg.
Neomycin	1,000 mg.
Polymyxin B	710,000 units
Water	sufficient to give 25 cc. of composition

This composition was placed in a two ounce Wheat Boston round glass bottle and pressured with nitrous oxide to a pressure of 90 psig. The bottle was provided with a metered valve to give 2.5 cc. doses. Thus there was sufficient material in the bottle to supply ten treatments for mastitis. The bottle after filling was provided with an overall coating of saran (a crystalline vinylidene chloride resin) which thus sealed all openings and joints. The saran coating was applied by dipping the filled bottle in a solution of Saran F-220 (vinylidene chloride-acrylonitrile copolymer) in a mixture of acetone and methyl ethyl ketone and allowing the solvent to dry. It was found that this saran coating greatly improved the shelf life of the mastitis composition.

When the udders of cows having mastitis were infused through the teats with this composition it was found that streptococci infections were 100% reduced and the staphylococci infections reduced over 40% after 120 hours of observation. There is no known mastitis preparation that is 100% effective against

staphylococcal mastitis and the results obtained with the compositions of the present invention compare favorably with those obtained with prior art compositions.

Example 2

One quarter from a cow was infused through the teat with one dose (2.5 cc.) of the aerosol composition prepared in Example 1 and another quarter of a different cow was infused with three 2.5 cc. doses of the aerosol composition of Example 1. Milk samples from the treated quarters were obtained after 24, 48, and 72 hours following treatment for antibiotic assay by the U.S.P. cylinder-plate method as outlined in Volume XV, pages 848-858 of the U.S. Pharmacopedia. The results of the one and three doses administered were as follows:

	Time After Instillation							
	1 Dose				3 Doses			
	5 hrs.	24 hrs.	48 hrs.	72 hrs.	5 hrs.	24 hrs.	48 hrs.	72 hrs.
Dihydro-streptomycin	8.5	5.5	0	0	9.1	7.5	5.3	0
Neomycin	6.6	4.39	0	0	7.4	5.6	4.3	0
Polymyxin B	52.9	0	0	0	65.3	45.7	0	0

The results for dihydrostreptomycin and neomycin are expressed in micrograms/ml. and the results for polymyxin B are expressed in units/ml.

Thus, there was no residue of any antibiotic in the milk 48 hours after the one dose treatment or after 72 hours in the three dose treatment. No untoward signs, such as irritation, were observed in any of the quarters treated with either one or three doses.

Example 3

The procedure of Example 2 was varied by giving the cows three 2.5 cc. doses 12 hours apart of the aerosol composition of Example 1. The first sample was taken 24 hours after the last dose was given. A total of 11 quarters on 6 different cows were used in this test. No dihydrostreptomycin or polymyxin was detected in the milk after 48 hours. Neomycin was detected in 2 quarters at the end of 48 hours, but at the end of 72 hours even the neomycin was no longer detected.

No residue of antibiotic was observed after 48 hours in any of 7 quarters of 3 cows given a single 2.5 cc. dose of the aerosol antibiotic composition of Example 1.

Example 4

A total of 164 quarters of 41 milk cows from 3 herds with a history of mastitis were examined clinically and the leucocyte content and bacterial content of milk samples were determined. Forty quarters were mastitic. At 12 hour intervals 29 of these mastitic quarters were given two 2.5 cc. doses of the aerosol composition of Example 1. Eleven quarters were infused with one 2.5 cc. dose. Eight of the quarters previously given one dose were infused with three 2.5 cc. doses at 12 hour intervals 17 days after the initial

treatment. Samples of the milk from all treated quarters were examined for leucocyte and bacterial content at 0, 24, 48, 72 and 120 hours post treatment, and at 17 days on the 11 quarters given one injection.

The results of this experiment were as follows:

1. At the 120 hour observation 93.1% of the streptococcus infections and 42.7% of the staphylococcus infections were eliminated by the various treatments.

2. The use of one 2.5 cc. dose eliminated 100% of the streptococci and 20% of the staphylococci in 11 quarters for the 17 days observed.

3. 120 hours following the last treatment milk samples from 29 quarters infused with two 2.5 cc. doses at 12 hour intervals showed a reduction of 88.2% streptococci and 41.6% of the staphylococci.

4. 120 hours following the last of 3 treatments with a 2.5 cc. dose there was a reduction by 25% in the staphylococcus infections in 8 quarters that did not respond to the one dose treatment given 17 days previously, making a total of 40% elimination of staphylococci and a 100% elimination of streptococci when the one dose recoveries are included.

5. The aerosol antibiotic composition was nontoxic and there were no symptoms of irritation. There was no flinching or kicking or other indications that cows objected to the udder infusion of the preparation.

Example 5

In order to improve the stability of the aerosol composition, there can be added conventional stabilizers. A typical formulation utilizing stabilizers is:

Dihydrostreptomycin	2,500 mg.
Neomycin	1,000 mg.
Polymyxin B	710,000 units
Methyl paraben	50 mg.
Propyl paraben	12.5 mg.
Distilled water	q.s. to make 2.5 cc.

The above formula was packaged in the 10 dose plastic coated bottles described in Example 1 with sufficient nitrous oxide at 90 psig. to propel approximately 2.5 cc. of finished product through the valve. This composition was used in the same manner as in Examples 1-4.

Example 6

This illustrates the preparation of a commercial batch sufficient for 10,000 bottles (100,000 doses).

Dihydrostreptomycin sulfate powder in an amount equivalent to 25 kilograms of the free base, neomycin sulfate powder in an amount equivalent to 10 kilograms of the free base, polymyxin B sulfate powder in an amount equivalent to 7.1 billion units, 500 grams of methyl paraben and 125 grams of propyl paraben were thoroughly mixed. Then water was added in an amount sufficient to give a total volume of 250 liters. The solution was warmed to 50°C. and

held for 10 to 15 minutes. 29 grams of this mixture were then poured into each 2 oz. Wheaton Boston round plastic-coated bottle as in Example 1. A metered Risdon valve (2.5 cc.) was attached to each bottle and nitrous oxide loaded through the valve until an equilibrium pressure of 90 psig. was attained in the bottle.

The final composition was stable for at least 51 days at 45°C. and for at least 87 days at room temperature.

While the use of saran coated bottles is preferred, metal cans and other conventional aerosol containers can be employed.

Disposable plastic teat tubes were employed with the aerosol container to infuse the cows in the examples, although other conventional test tubes can be employed.

The use of the aerosol composition as a therapeutic for the treatment of mastitis has numerous advantages over prior art procedures.

Thus, there is greater ease of application of the therapeutic in introducing it into the udder of the cow. Additionally, there is an efficient measured dose, permitting the faster treatment of the animal.

The propellant was observed to be a non-refrigerant with no irritating effect in cattle. The aerosol compositions also are suitable for infusing the mammary glands of other mammals, e.g., goats and sheep, by introduction of the antibiotic

through the teat.

The use of the overlay of nitrous oxide or other inert gas increases the stability of the antibiotics beyond that normally obtained in mastitis preparations.

Furthermore, there can be used a reduced dosage of a liquid preparation as compared with the prior art.

There is a beneficial increase of phagocytes and leucocytes following treatment which aids in rapid and natural healing. As a result, there is a more rapid return of the milk to its normal physical and chemical state. The leucocyte and phagocyte stimulation, however, is not sufficient to be an acute inflammatory reaction.

The infusion of nitrous oxide or other inert gas changes the oxygen tension of the udder to such a state that organisms requiring a free oxygen tension are inhibited greatly in function and reproduction.

As previously indicated, the novel combination of antibiotics set forth in the above examples is preferred. However, other mastitis treating formulations can be dispersed in a liquid vehicle and pressured with an inert gas to give aerosols. Typical of such less preferred compositions suitable for dispersion in water or other liquid vehicle and pressurizing are:

Composition A

Procaine Penicillin G	100,000 units
Dihydrostreptomycin Sulfate	100 mg.
Neomycin	100 mg.
Sulfisoxazole	5% by weight

Composition B

Procaine Penicillin G	100,000 units
Dihydrostreptomycin Sulfate	100 mg.
Sulfamerazine	10% (w/v)
Sulfathiazole	10% (w/v)

Dispersed in peanut oil containing 3% (w/v) aluminum stearate

Composition C

Procaine Penicillin G	100,000 units
Dihydrostreptomycin Sulfate	500 mg.
Neomycin	50 mg.
Sulfamerazine	5% (w/v)
Sulfathiazole	5% (w/v)
Sulfanilamide	10% (w/v)
Papain	50 mg.

Composition D

Streptomycin	1 part
Dihydrostreptomycin	1 part

Composition E

Neomycin Sulfate	400 mg.
Polymyxin B Sulfate	400,000 units
Methapyrilene hydrochloride	800 mg.

Composition F

Erythromycin	200 mg.
Streptomycin	200 mg.

Composition G

Procaine Penicillin G	10,000 units
Dihydrostreptomycin Sulfate (equivalent to dihydrostreptomycin)	10 mg.
Sulfisoxazole	75 mg.
Sulfathiazole	75 mg.
Cobalt Sulfate	0.5 mg.

Suspensed in peanut oil containing 3% (w/v) aluminum stearate

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A therapeutic composition or synergistic mixture effective in the treatment of mastitis of milk animals, by instillation into the animal mammary gland, the composition or synergistic mixture comprising streptomycin or dihydrostreptomycin, neomycin and polymyxin.

2. A composition or synergistic mixture according to claim 1, wherein the composition or mixture is dispersed in a nontoxic milk miscible liquid and a nontoxic pressure generating propellant.

3. A composition or synergistic mixture according to claim 2, wherein said liquid is an aqueous liquid.

4. A composition or synergistic mixture according to claim 2 or 3, wherein the propellant is pressured at between 25 to 150 psig and preferably at 90 psig.

5. A composition or synergistic mixture according to claims 2 or 3, wherein the propellant is nitrous oxide.

6. A composition or synergistic mixture according to claim 1, having 50 mg to 2,500 mg dihydrostreptomycin or streptomycin, 50 mg to 1,000 mg neomycin and 50,000 units to 1,000,000 units of polymyxin.

7. A composition or synergistic mixture according to claim 6, wherein such amounts as specified are dispersed in 1 to 30 c.c., and preferably 2.5 c.c., of water.

8. A composition or synergistic mixture according to claim 7, having 2,500 mg dihydrostreptomycin, 1,000 mg of neomycin, 710,000 units of poymyxin B and 2.5 c.c. of water.

9. A composition or synergistic mixture according to any one claims 6 to 8, including stabilizers consisting of 50 mg methyl paraben and 12.5 mg propyl paraben.

10. A process for making a therapeutic composition or synergistic mixture effective in the treatment of mastitis of milk animals by instillation into the animal mammary gland, which comprises the steps of mixing together streptomycin or dihydrostreptomycin, neomycin and polymycin.

11. A process according to claim 10 including the additional step of dispersing the composition or mixture in a nontoxic milk miscible liquid and a nontoxic pressure generating propellant.

12. A process according to claim 11 wherein said liquid is an aqueous liquid.

13. A process according to claim 12 wherein the propellant is pressured at 25 to 150 psig and preferably at 90 psig.

14. A process according to any one of claims 11 to 13, wherein the propellant is nitrous oxide.

15. A process according to claim 11, wherein there is mixed together 50 mg to 2,500 mg dihydrostreptomycin or streptomycin, 50 mg to 1,000 mg neomycin, and 50,000 units to 1,000,000 units of polymyxin.

16. A process according to claim 15 including the additional step of dispersing the mixture in 1 to 30 c.c., and preferably 2.5 c.c., of water.

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17. A process according to claim 16, mixing together 2,500 mg dihydostreptomycin, 1,000 mg of meomycin, 710,000 units of polymyxin B, and 2.5 c.c. of water.

18. A process according to any one of claims 15 to 17, including the additional step of adding stabilizers consisting of 50 mg methyl paraben and 12.5 mg propyl paraben.

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